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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P.ULB.33/WO		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/BE 96/00087	14/08/1996	15/08/1995
International Patent Classification (IPC) or national classification and IPC		
C12N15/12		
Applicant		
UNIVERSITE LIBRE DE BRUXELLES et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of 6 sheets.

3. This report contains indications and corresponding pages relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [X] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [X] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/02/1997	07.11.97
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	R. Großkopf
	Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.
PCT/BE96/00087

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

[ ] the international application as originally filed.

[x] the description, pages 1-26, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

[x] the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-34, filed with the letter of 13.08.97,
Nos. _____, filed with the letter of _____,

[x] the drawings, sheets/fig 1/11-11/11, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:
[ ] the description, pages _____.
[ ] the claims, Nos. _____.
[ ] the drawings, sheets/fig _____.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

[ ] the entire international application,

[x] claims Nos. 1-4,6-34

because:

[ ] the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination (specify):

[x] the description, claims or drawings (indicate particular elements below) or said claims Nos. 1-4,6-34 are so unclear that no meaningful opinion could be formed (specify):

The Applicant has isolated the ligand for the so-called "ORL_1 receptor" and a DNA encoding said ligand.
The subject-matter which takes into account of said finding might constitute a basis for novel and inventive claims (see also item V).
However, with the exception of one part of Claim 5 (i.e. the part which relates to the specific sequence) none of the claims corresponds to said finding in a suitable manner. Moreover, most of the claims relate to subject-matter which is neither clearly characterised nor sufficiently disclosed in the present application. Other claims relate to subject-matter the relevance of which is totally unclear and which, if maintained in the present application, would give rise to objections for lack of unity.

Thus Claims 1 to 3 relate to a nucleic acid molecule. As far as the broadening of said claims to either (not specified) "70% or 90%" or even "portions" thereof (and complementary sequences) is concerned (the scope of such

claims may result in nucleic acids which no longer encode the peptide of Claim 5), both the scope and the relevance of said claims is totally unclear.

In fact, with the exception of that portion (where is it located?) of the nucleic acid sequence which encodes the peptide according to Claim 5 (which corresponds to about 6% of said sequence i.e. 51 bp out of 932 bp) the relevance of other parts of said sequence is totally unclear. Although some parts may encode other possible peptides or reading frames (again they are not allocated in said sequence) including those according to Claims 7 and 8 the relevance of said possible reading frames is either speculative or totally unclear.

This applies especially for the (undefined) various possible peptides according to Claim 4.

However even as far as the peptide of claims 7 and 8 are concerned, the relevance of said peptides is also unclear. In addition, even if said peptides had a certain function, they would not be connected by a common (inventive) concept with the peptide of Claim 5 since they have neither a specific structural nor a functional relationship with the peptide of Claim 5.

As far as all peptide claims are concerned (further) "agonists" are neither (sufficiently) disclosed in the present application nor are said agonists characterised by any technical feature (the agonist of Claims 7 and 8 not even by a function).

The same applies again for the "inhibitors" of Claims 9 to 16.
Thus, in cases where said inhibitor are directed to a sufficiently characterised entity (e.g. of Claim 5) they are themselves not characterised. As far as they are di-

rected to entities which itself are not clearly defined (e.g. Claims 1 to 3), they are totally "meaningless".

Claims 17 to 22, being dependent claims could at best be clear as far as they relate to a clearly defined entity.

Further unclarities arise with the wording of Claims 23 to 30 which are directed to methods for isolating or recovering the undefined entities. Said claims could, at best, be accepted if they were drafted as "use" claims of an entity which is clearly defined (e.g. again the protein of Claim 5).

Finally, all of the objections mentioned above (clarity, insufficiency, lack of unity) also apply for the "compounds" according to Claim 31 and, consequently, also for the "pharmaceutical compositions" containing said compounds.

Thus, as indicated initially, this Authority could only see a basis for acceptable claims in the subject-matter which relate in a clearly defined manner to the ligand as defined in Claim 5.

[X] the claims, or said claims Nos. 1-34_____ are so inadequately supported by the description that no meaningful opinion could be formed.

[ ] no international search report has been established for said claims Nos. _____.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

[ ] restricted the claims.
[ ] paid additional fees.
[ ] paid additional fees under protest.
[ ] neither restricted nor paid additional fees.

2. [x] This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
[ ] complied with.
[ ] not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

[ ] all parts.
[ ] the parts relating to claims Nos. _____.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 5	YES
	Claims	NO
Inventive Step (IS)	Claims 5	YES
	Claims	NO
Industrial Applicability (IA)	Claims 5	YES
	Claims	NO

2. CITATIONS AND EXPLANATIONS

The peptide according to Claim 5 whose function has been identified by the Applicant is neither disclosed nor obviously derivable from the prior art.

CLAIMS

1. Nucleic acid molecule which corresponds to at least 70% of the SEQ ID NO. 1 or its complementary strand.

2. Nucleic acid molecule which corresponds to at least 90% of the SEQ ID NO. 1 or its complementary strand.

3. Isolated nucleic acid molecule comprising at least the SEQ ID NO. 1, its complementary strand or a portion thereof, having more than 15 nucleotides able to identify or reconstitute SEQ ID NO. 1 or its complementary strain.

4. Peptide encoded by the nucleic acid molecule according to any of the preceding claims.

5. Peptide according to the claim 4, having the following amino acid sequence of SEQ ID NO. 2 :
Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln, or agonists of its receptor(s).

6. Peptide according to the claim 5, characterized in that it is a ligand of the ORL_1 receptor, preferably a mammal ORL_1 receptor, more specifically the human ORL_1 receptor.

7. Peptide according to the claim 4, having the following amino acid sequence of SEQ ID NO. 3 :
Phe-Ser-Glu-Phe-Met-Arg-Gln-Tyr-Leu-Val-Leu-Ser-Met-Gln-Ser-Ser-Gln, or agonists of its receptor(s).

8. Peptide according to the claim 4, having the following amino acid sequence of SEQ ID NO. 4 :

Thr-Leu-His-Gln-Asn-Gly-Asn-Val, or agonists of its receptor(s).

9. Inhibitor directed against the nucleic acid molecule according to any of the claims 1 to 4, the peptide according to any of the claims 4 to 8 or the receptor(s) of said peptide.

10. Inhibitor according to the claim 9, characterized in that it is a polyclonal or monoclonal antibody or a portion thereof, directed against the peptide according to any of the claims 4 to 8 or its receptor.

11. Inhibitor according to the claim 9, which is an antisense oligonucleotide which has a sequence capable of specifically binding to the nucleic acid molecule according to any of the claims 1 to 3 so as to prevent its transcription and/or its translation.

12. Inhibitor according to the claim 11, comprising chemical analogs of nucleotides.

13. Inhibitor according to the claim 11, said oligonucleotides having sequences which differ from one another at predefined positions.

14. Inhibitor according to any of the claims 11 to 13, wherein the oligonucleotide is coupled to a substance which inactivates the nucleic acid according to any of the claims 1 to 3.

15. Inhibitor according to the claim 14, wherein said substance is a ribozyme.

16. Inhibitor according to the claim 9, characterized in that it is an antagonist to the receptor of the peptide according to any of the claims 4 to 8.

17. Vector comprising the nucleic acid molecule according to any of the claims 1 to 3.

18. Pharmaceutical composition comprising an element chosen among the group consisting of the nucleic acid molecule according to any of the claims 1 to 3, the peptide according to any of the claims 4 to 8, the inhibitor according to any of the claims 9 to 16 and/or the vector according to the claim 17, and a pharmaceutically acceptable carrier.

19. Pharmaceutical composition comprising an amount of a substance effective to reduce the expression and/or the "effects" resulting from expression of the peptide according to any of the claims 4 to 8, and a pharmaceutically acceptable carrier.

20. Pharmaceutical composition comprising an amount of a substance effective to reduce the expression and/or the "effects" resulting from expression of the nucleic acid molecule according to any of the claims 1 to 3.

21. Pharmaceutical composition according to any of the claims 18 to 20, for the treatment and/or the prevention of a disease related to the following functions and/or behaviours : hyperalgesia, neuroendocrine secretion, stress, locomotor activity, anxiety, instinctive behaviour, decreasing of learning, memory, curiosity, attention and/or sensory perception.

22. Transgenic non-human animal which comprises the nucleic acid molecule according to any of the claims 1 to 3.

23. Method for recovering an inhibitor not known to be capable of specifically binding to a peptide according to any of the claims 4 to 8 can specifically bind to it, which comprises contacting the peptide according to any of the claims 4 to 8 under conditions permitting

binding of a inhibitor known to bind the peptide according to any of the claims 4 to 8, determining the presence of any inhibitor bound to said peptide and recovering said inhibitor.

24. Method for recovering a compound not known to be capable of specifically binding as an antagonist or as an agonist of the peptide according to the claim 6 to a ORL_1 receptor, preferably a mammal ORL_1 receptor, specifically a human ORL_1 receptor, can specifically bind to said receptor, which comprises contacting a cell, preferably a mammalian cell, comprising a vector adapted for expression in a mammalian cell, which vector further comprises nucleic acid molecule which expresses said ORL_1 receptor on the cell's surface, with the compound under conditions permitting binding of the peptide known to bind to said receptor, detecting the presence of any compound bound to said receptor, and recovering said compound.

25. Method for recovering a compound not known to be capable of specifically binding as an antagonist or as an agonist of the peptide according to the claim 6 to an ORL_1 receptor, preferably a mammal ORL_1 receptor, specifically a human ORL_1 receptor, can specifically bind to said receptor, which comprises preparing a cell extract from cells, preferably of mammalian cells, which comprises a vector adapted for expression in said cells, which vector further comprises nucleic acid molecule which expresses said receptor on the cell's surface, isolating a membrane fraction from the cells extract, incubating the compound with the membrane fraction under conditions permitting the binding of the peptide known to bind to said receptor, detecting the

presence of any bound compound, and recovering said compound.

26. Method for recovering a compound which is not known to be capable of binding as an antagonist or as an agonist of the peptide according to the claim 6 to an ORL_1 receptor, preferably a mammal ORL_1 receptor, more specifically a human ORL_1 receptor, and prevent the peptide according to the claim 6, to activate said receptor, which comprises contacting a cell, preferably a mammalian cell, which cell comprising a vector adapted for expression in said cell, such vector further comprising nucleic acid molecule which expresses said receptor on the cell's surface with the compound under conditions permitting measure of a functional response, determining whether the compound prevents the peptide to activate said receptor, and recovering said compound.

27. Method according to the claim 24, wherein the cell is a non-neuronal cell, comprising the cellular components necessary to produce a second messenger and wherein the determination (of whether the compound blocks the activation of the ORL_1 receptor by a peptide according to the claim 6 or mimics inactivation of the ORL_1 receptor by a peptide according to the claim 6) comprises detecting the change in the concentration of the second messenger.

28. Method according to the claim 27, wherein the second messenger is chosen among the group consisting of cyclic AMP (cAMP), inositol phosphate metabolite or intracellular calcium.

29. Method according to the claim 28, wherein the modification of the second messenger is monitored by a secondary production of a report molecule chosen among the group consisting of luciferase, -galactosidase,

chloramphenicol acetyltransferase or grove hormone, or by the physiological modification of the cell, preferably monitored by measure of the extra-cellular pH.

30. Method according to any of the claims 27 to 29, wherein the non-neuronal cell is CHO.

31. Compound identified by the method according to any of the claims 23 to 30.

32. Pharmaceutical composition comprising the compound according to the claim 31 and a pharmaceutically acceptable carrier.

33. Diagnostic and/or dosage device comprising an inhibitor according to any of the claims 9 to 16, the peptide according to any of the claims 4 to 8 and possibly its receptor(s), preferably the ORL_1 receptor.

34. Method of genetic treatment or prevention of a disease induced by the nucleic acid sequence or the peptide according to any of the claims 1 to 8 in an animal, specifically in a human, wherein an inhibitor according to any of the claims 9 to 16 or a nucleic acid molecule encoding said inhibitor is administered to a patient with a pharmaceutically acceptable carrier to reduce the expression and/or the "effects" resulting from expression of said nucleic acid sequence or said peptide.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
OFFICE VAN MALDEREN
Attn. VAN MALDEREN, Eric
Place Reine Fabiola 6/1
1083 Bruxelles
BELGIUM

REÇU
-8.-1-1997
OFFICE VAN MALDEREN

Applicant's or agent's file reference P.ULB.33/WO	Date of mailing *(day/month/year)* 06/01/1997
International application No. PCT/BE 96/00087	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant UNIVERSITE LIBRE DE BRUXELLES et al.	International filing date *(day/month/year)* 14/08/1996

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zorka Bota

Form PCT/ISA/220 (January 1994)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P.ULB.33/WO		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/BE 96/00087	14/08/1996	15/08/1995
Applicant		
UNIVERSITE LIBRE DE BRUXELLES et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [X] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. 9
   - [X] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 96/00087

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C12N15/11 C07K14/665 C07K16/18 A61K38/17
A61K48/00 A01K67/027 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 01548 (MEDICAL RES COUNCIL ;SIBSON DAVID ROSS (GB); GROSS JACQUELINE (GB)) 20 January 1994 see claims 1-19; figure SEQ.ID.491 ---	1,3,4
Y	FEBS LETT, MAR 14 1994, 341 (1) P33-8, NETHERLANDS, XP002020079 MOLLEREAU C ET AL: "ORL1, a novel member of the opioid receptor family. Cloning, functional expression and localization." see the whole document ---	1-6, 9-14, 16-26, 32-34
Y	WO,A,95 12616 (SLOAN KETTERING INST CANCER) 11 May 1995 see claims 1-46 --- -/--	1-6, 9-14, 16-21, 23-26, 32,33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 December 1996	06. 01. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Gurdjian, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 21309 (LEE NANCY M ;LOH HORACE H (US); LIPPMAN DAVID (US)) 28 October 1993 see claims 1-14	22,34
P,X	NATURE, OCT 12 1995, 377 (6549) P532-5, ENGLAND, XP002020080 MEUNIER JC ET AL: "Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor " see the whole document	1-9
P,X	BIOCHEM BIOPHYS RES COMMUN, DEC 14 1995, 217 (2) P539-45, UNITED STATES, XP002020081 SAITO Y ET AL: "N23K, a gene transiently up-regulated during neural differentiation, encodes a precursor protein for a newly identified neuropeptide nociceptin." see the whole document	1-9
P,X	BR. J. PHARMACOL., 1996, 117, 1609-11, XP000611201 VAUGHAN, CHRISTOPHER W. ET AL: "Increase by the ORL1 receptor (opioid receptor-like1) ligand, nociceptin, of inwardly rectifying K conductance in dorsal raphe nucleus neurons" see the whole document	1-9
P,X	J BIOL CHEM, SEP 29 1995, 270 (39) P22772-6, UNITED STATES, XP002020083 ZHANG S ET AL: "Identification of dynorphins as endogenous ligands for an opioid receptor-like orphan receptor." see the whole document	1-9
P,X	SCIENCE, NOV 3 1995, 270 (5237) P792-4, UNITED STATES, XP002020234 REINSCHEID RK ET AL: "Orphanin FQ: a neuropeptide that activates an opioidlike G protein-coupled receptor." see the whole document	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/BE 96/00087

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9401548	20-01-94	AU-A-	4512193	31-01-94
		EP-A-	0587279	16-03-94
WO-A-9512616	11-05-95	AU-A-	1089095	23-05-95
WO-A-9321309	28-10-93	AU-A-	4276993	18-11-93
		CA-A-	2117756	28-10-93
		EP-A-	0643768	22-03-95
		JP-T-	8501442	20-02-96
		NO-A-	943808	06-12-94

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

REÇU
23. -9- 1996
OFFICE VAN MALDE

To:

VAN MALDEREN, Eric
Office Van Malderen
Place Reine Fabiola 6/1
B-1083 Bruxelles
BELGIQUE

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
12 September 1996 (12.09.96)	
Applicant's or agent's file reference	**International application No.**
P.ULB.33/WO	PCT/BE96/00087

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

UNIVERSITE LIBRE DE BRUXELLES (for all designated States except US)
PARMENTIER, Marc et al (for US)

International filing date	:	14 August 1996 (14.08.96)
Priority date(s) claimed	:	15 August 1995 (15.08.95)
Date of receipt of the record copy by the International Bureau	:	11 September 1996 (11.09.96)
List of designated Offices	:	

EP :AT,BE,CH,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
National :CA,JP,US

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase;
- [X] confirmation of precautionary designations;
- [ ] requirements regarding priority documents.

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Catherine Massetti

Telephone No. (41-22) 730.91.11

International application No.
PCT/BE96/00087

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiry of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

Note that since ES and GR are not bound by PCT Chapter II (which provides for the international preliminary examination procedure), those States cannot be elected in a demand for international preliminary examination. In the case of the designation of ES for a national patent, the applicant must thus always enter the national phase before the national Office of that State before the expiry of 20 months from the priority date. In the case of the designation of ES or GR for a European patent, however, the 31-month time limit applies in respect of those designations if at least one other State designated for a European patent is also elected within the 19-month period.*

Note also that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

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* CH and LI became bound by PCT Chapter II on 1 September 1995. Therefore, CH and LI may be elected in a demand or a later election filed on or after that date, regardless of the filing date of the international application. (See 2nd paragraph above.)

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents the following is recalled.

Where the priority of an earlier national (i.e., national or regional) application is claimed, the applicant must submit a copy of the said national application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date (Rule 17.1).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such a request must be made before the expiration of the 16-month time limit.

It is recalled that, where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

If the priority document concerned is not submitted to the International Bureau before the expiration of the 16-month time limit, or if the request to the receiving Office to transmit the priority document has not been made (and the corresponding fee, if any, paid) before the expiration of this time limit, any designated State may disregard the priority claim.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

VAN MALDEREN, Eric
Office Van Malderen
Place Reine Fabiola 6/1
B-1083 Brussels
BELGIQUE

Date of mailing (day/month/year) 13 March 1997 (13.03.97)	
Applicant's or agent's file reference P.ULB.33/WO	**IMPORTANT INFORMATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/BE96/00087	14 August 1996 (14.08.96)	15 August 1995 (15.08.95)

Applicant
UNIVERSITE LIBRE DE BRUXELLES et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP :AT,BE,CH,DE,DK,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :CA,JP,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   None

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of the annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent including, where applicable, ES which cannot be elected since it is not bound by Chapter II.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Catherine Massetti

Telephone No. (41-22) 730.91.11

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
OFFICE VAN MALDEREN
Attn. VAN MALDEREN, Eric
Place Reine Fabiola 6/1
B-1083 Bruxelles
BELGIUM

NOTIFICATION OF RECEIPT OF SEARCH COPY

(Pct Rule 25.1)

Date of mailing *(day/month/year)*	01/10/96
Applicant's or agent's file reference: P.ULB.33/WO	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	(Priority date) *(day/month/year)*
PCT/BE 96/00087	14/08/96	15/08/95

Applicant

UNIVERSITE LIBRE DE BRUXELLES et al.

1. **Where the International Searching Authority and the receiving Office are not the same Office:**

   The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below.

   Where the International Searching Authority and the receiving Office are the same Office:

   The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

   12/09/96 *(date of receipt)*.

2. **Time limit for establishment of international search report**

   The applicant is informed that the time limit for establishing the international search report is 3 months from the date of receipt indicated above or 9 months from the priority date, whichever time limit expires later

3. A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the receiving Office.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ISA/EP

Form PCT/ISA/202 (July 1992)

PATENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OF PRIORITY DOCUMENTS

(PCT Administrative Instructions, Section 411)

To:

VAN MALDEREN, Eric
Office Van Malderen
Place Reine Fabiola 6/1
B-1083 Bruxelles
BELGIQUE

Date of mailing (day/month/year)
12 September 1996 (12.09.96)

Applicant's or agent's file reference
P.ULB.33/WO

IMPORTANT NOTIFICATION

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/BE96/00087	14 August 1996 (14.08.96)	15 August 1995 (15.08.95)

Applicant
UNIVERSITE LIBRE DE BRUXELLES et al

The applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to the following application(s):

Priority application No:	Priority date:	Priority country:	Date of receipt of priority document:
60/002,368	15 Aug 1995 (15.08.95)	US	11 Sep 1996 (11.09.96)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Catherine Massetti

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
VAN MALDEREN, Eric
OFFICE VAN MALDEREN
Place Reine Fabiola 6/1
1083 Bruxelles
BELGIQUE

REÇU
-6.-2-1997
OFFICE VAN MALDEREN

NOTIFICATION OF RECEIPT OF DEMAND

(PCT Rule 61.1(b), first sentence and Administrative Instructions, Section 601)

Date of mailing *(day/month/year)*	04.03.97
Applicant's or agent's file reference: P.ULB.33/WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BE 96/00087	14/08/1996	15/08/1995

Applicant

UNIVERSITE LIBRE DE BRUXELLES et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

   24/02/1997

2. This date of receipt is:

   [Y] the actual date of receipt of the demand.

   [ ] the date on which the proper corrections to the demand were timely received.

3. [ ] This date is **AFTER** the expiration of 19 months from the priority date.

   Attention: The election(s) made in the demand does (do) not have the effect of postponing the commencement of the national phase until 30 months from the priority date (or later in some Offices)(Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22).

   For details, see Annex B to Form PCT/IB/301 sent by the International Bureau and Volume II of the PCT Applicant's Guide.

   [ ] This notification confirms the information given in person or by telephone on:

   _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich. Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	E. Crane Telephone No. 2648

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: P.ULB.33/WO

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/BE96/00087	14 August 1996	15 August 1995

Title of invention: NUCLEIC ACID MOLECULES ENCODING PEPTIDES HAVING PRONOCICEPTIVE PROPERTIES

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

UNIVERSITE LIBRE DE BRUXELLES
Avenue F.D. Roosevelt 50
B-1050 BRUSSELS
BELGIUM

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(i.e. country)* of nationality: BE

State *(i.e. country)* of residence: BE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PARMENTIER Marc
chaussée d'Uccle, 304
B-1630 LINKEBEEK
BELGIUM

State *(i.e. country)* of nationality: BE

State *(i.e. country)* of residence: BE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

VASSART Gilbert
Avenue Lambeau 113
B-1200 BRUSSELS
BELGIUM

State *(i.e. country)* of nationality: BE

State *(i.e. country)* of residence: BE

[X] Further applicants are indicated on a continuation sheet.

International application No.
PCT/BE96/00087

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet is not to be included in the demand.

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

MEUNIER Jean-Claude
Lotissement du Pin 8
F-31320 REBIGUE
FRANCE

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
FR	FR

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

MOLLEREAU Catherine
Chemin des Saules 15
F-31320 CASTANET
FRANCE

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:
FR	FR

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(i.e. country)* of nationality:	State *(i.e. country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/BE96/00087

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

VAN MALDEREN Eric
OFFICE VAN MALDEREN
Place Reine Fabiola 6/1
B-1083 BRUSSELS
BELGIUM

Telephone No.: 32 2 4263810

Facsimile No.: 32 2 426 37 60

Teleprinter No.:

[ ] Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the International Preliminary Examining Authority*

(i) [X] to start the international preliminary examination on the basis of the international application as originally filed.

(ii) [ ] to take into account the amendments under Article 34 of

- [ ] the description (amendments attached).
- [ ] the claims (amendments attached).
- [ ] the drawings (amendments attached).

(iii) [ ] to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).

(iv) [ ] to disregard any amendments of the claims made under Article 19 and to consider them as reversed.

(v) [ ] to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Box No. V ELECTION OF STATES

[X] The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* except .....

(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

International application No.
PCT/BE96/00087

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. amendments under Article 34				
description	:	sheets	☐	☐
claims	:	sheets	☐	☐
drawings	:	sheets	☐	☐
2. letter accompanying amendments under Article 34	:	sheets	☐	☐
3. copy of amendments under Article 19	:	sheets	☐	☐
4. copy of statement under Article 19	:	sheets	☐	☐
5. other *(specify)*:	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☒ fee calculation sheet
5. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

VAN MALDEREN Eric

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
VAN MALDEREN, Eric
OFFICE VAN MALDEREN
Place Reine Fabiola 6/1
1083 Bruxelles
BELGIQUE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	07. 11. 97

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
P.ULB.33/WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BE 96/00087	14/08/1996	15/08/1995

Applicant

UNIVERSITE LIBRE DE BRUXELLES et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	C. Vullo Telephone No. 8052

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/BE96/00087
International Application No.

14 AOU. 1996 (14-08-1996)
International Filing Date

RO/BE - PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* P.ULB.33/WO

Box No. I TITLE OF INVENTION NUCLEIC ACID MOLECULES ENCODING PEPTIDES HAVING PRONOCICEPTIVE PROPERTIES

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

UNIVERSITE LIBRE DE BRUXELLES
Avenue F.D. Roosevelt 50
B-1050 BRUSSELS
BELGIUM

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: [BELGIUM] BE

State *(i.e. country)* of residence: [BELGIUM] BE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PARMENTIER Marc
Chaussée d'Uccle, 304
B-1630 LINKEBEEK
BELGIUM

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: [BELGIUM] BE

State *(i.e. country)* of residence: [BELGIUM] BE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

VAN MALDEREN Eric
OFFICE VAN MALDEREN
Place Reine Fabiola 6/1
B-1083 BRUSSELS
BELGIUM

Telephone No. 02/4263810

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Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: BE [BELGIUM]

State *(i.e. country)* of residence: BE [BELGIUM]

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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- [X] applicant and inventor
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State *(i.e. country)* of residence: FR [FRANCE]

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
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- [ ] the States indicated in the Supplemental Box

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- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: FR [FRANCE]

State *(i.e. country)* of residence: FR [FRANCE]

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. VI PRIORITY CLAIM Further priority claims indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) [UNITED STATES OF AMERICA] US	(15/08/1995) 15 August 1995	60/002 368	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☐ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : _____

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA /_____

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request.*

Country (or regional Office): Date *(day/month/year)*: Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	:	5 sheets
2. description	:	26 sheets
3. claims	:	6 sheets
4. abstract	:	1 sheets
5. drawings	:	11 sheets
Total	:	49 sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☒ priority document(s) *identified in Box No. VI as item(s):*
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☐ other *(specify)*:

Figure No. 9 of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

VAN MALDEREN Eric

For receiving Office use only

1. Date of actual receipt of the purported international application: 14 AOU.1996 (14-08-1996)
2. Drawings: ☒ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted]E 96/00087

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C12N15/11 C07K14/665 C07K16/18 A61K38/17
A61K48/00 A01K67/027 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 01548 (MEDICAL RES COUNCIL ;SIBSON DAVID ROSS (GB); GROSS JACQUELINE (GB)) 20 January 1994 see claims 1-19; figure SEQ.ID.491 ---	1,3,4
Y	FEBS LETT, MAR 14 1994, 341 (1) P33-8, NETHERLANDS, XP002020079 MOLLEREAU C ET AL: "ORL1, a novel member of the opioid receptor family. Cloning, functional expression and localization." see the whole document ---	1-6, 9-14, 16-26, 32-34
Y	WO,A,95 12616 (SLOAN KETTERING INST CANCER) 11 May 1995 see claims 1-46 --- -/--	1-6, 9-14, 16-21, 23-26, 32,33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

3

Date of the actual completion of the international search	Date of mailing of the international search report
4 December 1996	06. 01. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Gurdjian, D

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PC[redacted]E 96/00087

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 21309 (LEE NANCY M ;LOH HORACE H (US); LIPPMAN DAVID (US)) 28 October 1993 see claims 1-14	22,34
P,X	NATURE, OCT 12 1995, 377 (6549) P532-5, ENGLAND, XP002020080 MEUNIER JC ET AL: "Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor " see the whole document	1-9
P,X	BIOCHEM BIOPHYS RES COMMUN, DEC 14 1995, 217 (2) P539-45, UNITED STATES, XP002020081 SAITO Y ET AL: "N23K, a gene transiently up-regulated during neural differentiation, encodes a precursor protein for a newly identified neuropeptide nociceptin." see the whole document	1-9
P,X	BR. J. PHARMACOL., 1996, 117, 1609-11, XP000611201 VAUGHAN, CHRISTOPHER W. ET AL: "Increase by the ORL1 receptor (opioid receptor-like1) ligand, nociceptin, of inwardly rectifying K conductance in dorsal raphe nucleus neurons" see the whole document	1-9
P,X	J BIOL CHEM, SEP 29 1995, 270 (39) P22772-6, UNITED STATES, XP002020083 ZHANG S ET AL: "Identification of dynorphins as endogenous ligands for an opioid receptor-like orphan receptor." see the whole document	1-9
P,X	SCIENCE, NOV 3 1995, 270 (5237) P792-4, UNITED STATES, XP002020234 REINSCHEID RK ET AL: "Orphanin FQ: a neuropeptide that activates an opioidlike G protein-coupled receptor." see the whole document	1-9

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/BE 96/00087

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9401548	20-01-94	AU-A- 4512193	31-01-94
		EP-A- 0587279	16-03-94
WO-A-9512616	11-05-95	AU-A- 1089095	23-05-95
WO-A-9321309	28-10-93	AU-A- 4276993	18-11-93
		CA-A- 2117756	28-10-93
		EP-A- 0643768	22-03-95
		JP-T- 8501442	20-02-96
		NO-A- 943808	06-12-94

P ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

VAN MALDEREN, Eric
Office Van Malderen
Place Reine Fabiola 6/1
B-1083 Brussels
BELGIQUE

Date of mailing (day/month/year)	
27 February 1997 (27.02.97)	
Applicant's or agent's file reference P.ULB.33/WO	**IMPORTANT NOTICE**

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/BE96/00087	14 August 1996 (14.08.96)	15 August 1995 (15.08.95)

Applicant
UNIVERSITE LIBRE DE BRUXELLES et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   CA,EP,JP,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   None

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   27 February 1997 (27.02.97) under No. WO 97/07205

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 730.91.11

Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
27 February 1997 (27.02.97)	
Applicant's or agent's file reference	**International application No.**
P.ULB.33/WO	PCT/BE96/00087

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

M. Van Malderen, Lic. A. C. Lg
E. Meyers, Phys. Dipl. EPZF
J. Van Malderen, Ir. Civ. Phys.
CONSEILS EN BREVETS EUROPÉENS

E. Van Malderen, Lic. Sc. Biol.
(Diplôme C.E.I.P.I. Brevets)
M. Stanislaus, Lic. Droit

(* = mandataire agréé Belgique)
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T.V.A. BE 416.281.637

Please reply to/Veuillez répondre à

EUROPEAN PATENT OFFICE
D-80298 MUNICH
GERMANY

Brussels, 13 August 1997.

Re.: International Patent Application No. PCT/BE96/00087
of August 14, 1996
in the name of UNIVERSITE LIBRE DE BRUXELLES et al.
for "NUCLEIC ACID MOLECULE ENCODING PEPTIDES ..."

Y. Ref. :

O. Ref. : P.ULB.33/WO

[redacted]

Dear Sirs :

We refer to the First Notification dated May 27, 1997, issued by th International Preliminary Examination Authority for the above-identified case.

The Applicant presents a new set of claims wherein the claim 3 has been amended.

Based upon this new set of claims, the Applicant presents the following comments.

1. Claims 1 - 3

In its Official Action, the Examiner states that the ligand which is described in the claim 5 should be the only subject matter taken into account as an invention, which may constitute basis for novel and inventive claims.

According to the Examiner, most of the other claims are r lated to subject matters which are neither clearly characterised nor sufficiently disclosed in the patent application.

The first aspect of the present invention is related to a new nucleic acid molecule identified as SEQ ID NO 1.

The pr sent invention pr tects als the variants of said nucl ic acid molecule (having more than 70%, preferably more than 90%, homology with said nucl ic acid molecule).

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The present invention is also related to portions of said nucl ic acid molecule, which means any nucleic acid molecule which is specific of the sequence SEQ ID. NO. 1. Said portions of nucleic acid molecule could be a probe or a primer which can be used to identify or reconstitute said sequence, for instance by gen tic amplification or by specific probe hybridisation.

In order to clarify the terms "portions of the isolated nucleic acid molecule", the Applicant presents an amendment to the claim 3, which finds a support in the specification, lines 18 to 27 of page 2.

A first industrial application of the nucleic acid sequence SEQ ID NO 1 or its complementary strain is the identification of patients which may present a genetic modification of said nucleic acid molecule, which may reduce the expression and/or the "effects" resulting from the expression of the peptide or the nucleic acid molecule according to the invention.

Another industrial application of the nucleotidic sequence SEQ ID NO 1 according to the invention consists into the preparation of an inhibitor directed against the whole nucleic acid molecule according to the invention or a portion thereof, in order to av id its translation (see first paragraph of page 4 and claim 34).

A specific example of said inhibitor is an anti-sens oligonucleotide which has a sequence capable of specifically binding to the whole nucleic acid molecule SEQ ID NO 1 or a portion th r of, so as to prevent its expression, transcription and/or translati n (see page 4, lines 17-28).

These inhibitors can also be directed against the variants of the nucleic acid sequence according to the invention (see claim 1 r 2).

2. Claim 4

As explained in the specification, several peptides are enc d d by the nucleic acid molecule SEQ ID NO 1, which can be ither precursors of active peptides or an active peptide having preferably nociceptive properties.

The precursor is the prepronociceptine which can be clived into various active peptid s (see pag 2, line 28 to page 3, lin 18).

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Therefore, the peptides encoded by the new nucleic acid molecul according to the invention can be either a precursor, or the peptide according to the claim 5 and/or 6, the peptide according to the claim 7 or 8.

3. Claims 5 and 6

The Examiner states that the claims related to the nucleic acid molecule (claims 1 to 3) may result in nucleic acids which n longer encode the peptide according to the claim 5 or 6.

However, the claim 5 is dependent on the claim 4, and is related to a specific embodiment of the present invention.

Other specific embodiments of the present invention which are dependent on the claim 4 are the peptide described in the claim 7 or 8.

In addition, the man skilled in the art is able to identify oth r variants of the peptide according to the invention which fall under the definition of claim 4.

4. Claims 7 and 8

As mentioned above, these claims are related to specific embodiments which fall under the definition of claim 4.

The Examiner states that the definition of the claims 7 and 8 ar unclear. In addition, he states that these claims relate to peptide of uncertain function, which do not present a common inventive concept with the peptide of the claim 5.

However, these peptides are encoded by the same nucleic acid molecule (nucleic acid molecule as defined in the claims 1 to 3), and correspond to the same precursor as described in th specification, last paragraph of page 2 and first paragraph f page 3).

In addition, it seems that these peptides present also no iceptive properties like the peptides of claim 5.

Therefore, thes peptides could also be used in the treatment and/ r th prevention of specific diseases as described in the sp cification (claim 21) or f r th screening f molecules which can be used for the treatment and/or the prevention of said diseases.

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5. Claims 9 - 16

These claims are related to inhibitors which may be directed against the nucleic acid molecule according to the invention, the peptide r their receptor.

Specific examples of said inhibitor are antagonists of the peptide according to the invention.

The Examiner states that the claims related to the agonists r antagonists of the peptide according to the invention are not sufficiently disclosed in the present patent application.

The Applicant disagrees with this objection of the Examiner.

Indeed, the man skilled in the art is able to identify the agonists and/or antagonists of the peptide according to the inventi n. The identification of said inhibitors or agonists of the peptide can b done by methods well known by the man skilled in the art, especially the one described in the specification on pages 6 to 8.

6. Claims 18 - 21

The man skilled in the art is also able to prepare the pharmaceutical composition described in the claims 18 to 21, wh rein the dosage of the active ingredients in the pharmac utic l composition may vary according to the pharmaceutically acceptabl carrier used, the patient treated and the side-effects of said active ingredient (see specification page 5, lines 17-20).

7. Claims 17 and 22

The man skilled in the art is also able to prepare according to his general knowledge the vector according to the claim 17 and the transgenic non-human mammal described in the claim 22.

8. Claims 23 - 30

The Examiner presents objections against the claims 23 to 30, which are directed to methods for isolating or recovering the agonists or inhibitors of the peptides according to the invention.

The Examiner propos s to amend these claims into us claims, preferably dependent on the claim 5.

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However, for the above-mentioned reasons, the Applicant would like to maintain these method claims. In addition, as specific Patent Offices, especially the US Patent and Trademark Office, do not accept use claims, the Applicant would like to maintain these claims without amending them.

9. Novelty and inventive step of the claims

According to the Applicant, it seems that the nucleic acid molecule according to any of the claims 1 to 3 has not been described in the state of the art.

In addition, it seems that none of the documents describes the amino acid sequence encoded by any of the nucleic acid molecules which correspond to the definition of the claims 1 to 3.

Moreover, none of the documents of the state of the art has described the use of said nucleic acid sequence.

Therefore, the nucleic acid molecule according to any of the claims 1 to 3 and the product or the method described in the dependent claims 4 to 34 are new and non-obvious in view of the state of the art.

Therefore, for the above-identified reasons, the Applicant requires a positive opinion from the Examiner about the novelty, the inventive step and the industrial application of the enclosed set of claims.

Meanwhile we remain,
Very truly yours,

OFFICE VAN MALDEREN

Eric Van Malderen
EVM/KDC

CLAIMS

1. Nucleic acid molecule which corresponds to at least 70% of the SEQ ID NO. 1 or its complementary strand.

2. Nucleic acid molecule which corresponds to at least 90% of the SEQ ID NO. 1 or its complementary strand.

3. Isolated nucleic acid molecule comprising at least the SEQ ID NO. 1, its complementary strand or a portion thereof, having more than 15 nucleotides able to identify or reconstitute SEQ ID NO. 1 or its complementary strain.

4. Peptide encoded by the nucleic acid molecule according to any of the preceding claims.

5. Peptide according to the claim 4, having the following amino acid sequence of SEQ ID NO. 2 : Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln, or agonists of its receptor(s).

6. Peptide according to the claim 5, characterized in that it is a ligand of the ORL_1 receptor, preferably a mammal ORL_1 receptor, more specifically the human ORL_1 receptor.

7. Peptide according to the claim 4, having the following amino acid sequence of SEQ ID NO. 3 : Phe-Ser-Glu-Phe-Met-Arg-Gln-Tyr-Leu-Val-Leu-Ser-Met-Gln-Ser-Ser-Gln, or agonists of its receptor(s).

8. Peptide according to the claim 4, having the following amino acid sequence of SEQ ID NO. 4 :

Thr-Leu-His-Gln-Asn-Gly-Asn-Val, or agonists of its receptor(s).

9. Inhibitor directed against the nucleic acid molecule according to any of the claims 1 to 4, the peptide according to any of the claims 4 to 8 or the receptor(s) of said peptide.

10. Inhibitor according to the claim 9, characterized in that it is a polyclonal or monoclonal antibody or a portion thereof, directed against the peptide according to any of the claims 4 to 8 or its receptor.

11. Inhibitor according to the claim 9, which is an antisense oligonucleotide which has a sequence capable of specifically binding to the nucleic acid molecule according to any of the claims 1 to 3 so as to prevent its transcription and/or its translation.

12. Inhibitor according to the claim 11, comprising chemical analogs of nucleotides.

13. Inhibitor according to the claim 11, said oligonucleotides having sequences which differ from one another at predefined positions.

14. Inhibitor according to any of the claims 11 to 13, wherein the oligonucleotide is coupled to a substance which inactivates the nucleic acid according to any of the claims 1 to 3.

15. Inhibitor according to the claim 14, wherein said substance is a ribozyme.

16. Inhibitor according to the claim 9, characterized in that it is an antagonist to the receptor of the peptide according to any of the claims 4 to 8.

17. Vector comprising the nucleic acid molecule according to any of the claims 1 to 3.

18. Pharmaceutical composition comprising an element chosen among the group consisting of the nucleic acid molecule according to any of the claims 1 to 3, the peptide according to any of the claims 4 to 8, the inhibitor according to any of the claims 9 to 16 and/or the vector according to the claim 17, and a pharmaceutically acceptable carrier.

19. Pharmaceutical composition comprising an amount of a substance effective to reduce the expression and/or the "effects" resulting from expression of the peptide according to any of the claims 4 to 8, and a pharmaceutically acceptable carrier.

20. Pharmaceutical composition comprising an amount of a substance effective to reduce the expression and/or the "effects" resulting from expression of the nucleic acid molecule according to any of the claims 1 to 3.

21. Pharmaceutical composition according to any of the claims 18 to 20, for the treatment and/or the prevention of a disease related to the following functions and/or behaviours : hyperalgesia, neuroendocrine secretion, stress, locomotor activity, anxiety, instinctive behaviour, decreasing of learning, memory, curiosity, attention and/or sensory perception.

22. Transgenic non-human animal which comprises the nucleic acid molecule according to any of the claims 1 to 3.

23. Method for recovering an inhibitor not known to be capable of specifically binding to a peptide according to any of the claims 4 to 8 can specifically bind to it, which comprises contacting the peptide according to any of the claims 4 to 8 under conditions permitting

binding f a inhibitor known to bind the p ptide according to any of the claims 4 to 8, determining the presence of any inhibitor bound to said peptide and recovering said inhibitor.

24. Method for recovering a compound not known to be capable of specifically binding as an antagonist or as an agonist of the peptide according to the claim 6 to a ORL_1 receptor, preferably a mammal ORL_1 receptor, specifically a human ORL_1 receptor, can specifically bind to said receptor, which comprises contacting a cell, preferably a mammalian cell, comprising a vector adapted for expression in a mammalian cell, which vector further comprises nucleic acid molecule which expresses said ORL_1 receptor on the cell's surface, with the compound under conditions permitting binding of the peptide known to bind to said receptor, detecting the presence of any compound bound to said receptor, and recovering said compound.

25. Method for recovering a compound not known to be capable of specifically binding as an antagonist or as an agonist of the peptide according to the claim 6 to an ORL_1 receptor, preferably a mammal ORL_1 receptor, specifically a human ORL_1 receptor, can specifically bind to said receptor, which comprises preparing a cell extract from cells, preferably of mammalian cells, which comprises a vector adapted for expression in said cells, which vector further comprises nucleic acid molecule which expresses said receptor on th cell's surface, isolating a membrane fraction from the cells xtract, incubating the compound with the membrane fraction under conditions permitting the binding of the peptide known to bind to said receptor, detecting the

presence of any bound compound, and recovering said compound.

26. Method for recovering a compound which is not known to be capable of binding as an antagonist or as an agonist of the peptide according to the claim 6 to an ORL_1 receptor, preferably a mammal ORL_1 receptor, more specifically a human ORL_1 receptor, and prevent the peptide according to the claim 6, to activate said receptor, which comprises contacting a cell, preferably a mammalian cell, which cell comprising a vector adapted for expression in said cell, such vector further comprising nucleic acid molecule which expresses said receptor on the cell's surface with the compound under conditions permitting measure of a functional response, determining whether the compound prevents the peptide to activate said receptor, and recovering said compound.

27. Method according to the claim 24, wherein the cell is a non-neuronal cell, comprising the cellular components necessary to produce a second messenger and wherein the determination (of whether the compound blocks the activation of the ORL_1 receptor by a peptide according to the claim 6 or mimics inactivation of the ORL_1 receptor by a peptide according to the claim 6) comprises detecting the change in the concentration of the second messenger.

28. Method according to the claim 27, wherein the second messenger is chosen among the group consisting of cyclic AMP (cAMP), inositol phosphate metabolite r intracellular calcium.

29. Method according to the claim 28, wherein the m dification of the sec nd messenger is monitored by a secondary production of a report molecule chosen among the group consisting of luciferase, -galactosidas ,

chloramphenicol acetyltransferase or grove hormone, or by the physiological modification of the cell, preferably monitored by measure of the extra-cellular pH.

30. Method according to any of the claims 27 to 29, wherein the non-neuronal cell is CHO.

31. Compound identified by the method according to any of the claims 23 to 30.

32. Pharmaceutical composition comprising the compound according to the claim 31 and a pharmaceutically acceptable carrier.

33. Diagnostic and/or dosage device comprising an inhibitor according to any of the claims 9 to 16, the peptide according to any of the claims 4 to 8 and possibly its receptor(s), preferably the ORL_1 receptor.

34. Method of genetic treatment or prevention of a disease induced by the nucleic acid sequence or the peptide according to any of the claims 1 to 8 in an animal, specifically in a human, wherein an inhibitor according to any of the claims 9 to 16 or a nucleic acid molecule encoding said inhibitor is administered to a patient with a pharmaceutically acceptable carrier to reduce the expression and/or the "effects" resulting from expression of said nucleic acid sequence or said peptide.

PATENT COOPERATION TREA[illegible]

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 13 March 1997 (13.03.97)	
International application No. PCT/BE96/00087	**Applicant's or agent's file reference** P.ULB.33/WO
International filing date (day/month/year) 14 August 1996 (14.08.96)	**Priority date** (day/month/year) 15 August 1995 (15.08.95)
Applicant PARMENTIER, Marc et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   24 February 1997 (24.02.97)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
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